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10/566,094	10/03/2006	Ramon Merce Vidal	284057US0PCT	9552
22850 7590 10/01/2009 OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314				
EXAMINER RICCI, CRAIG D				
ART UNIT		PAPER NUMBER		
1614				
NOTIFICATION DATE		DELIVERY MODE		
10/01/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/566,094

Applicant(s)

MERCE VIDAL ET AL.

Examiner

CRAIG RICCI

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 18, 19, 46, 47 and 74-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-14, 18, 19, 46, 47, 74-82, 84-90, 92 and 93 is/are rejected.
- 7) ☒ Claim(s) 83 and 91 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of the Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/21/2009 has been entered.

Response to Arguments



2. Applicants' arguments, filed 8/21/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

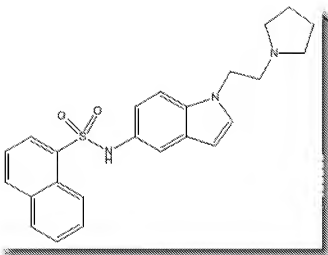
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 1-14, 18, 19, 46, 47, 74-82, 84-90, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Merce-Vidal et al* (cited in a previous Action) and *Filla et al* (cited in a previous Action).**

6. The instant invention is drawn to compounds which are useful as 5-HT₆ modulators. Specifically, instant claim 1 is drawn to compounds of formula (Ia) which encompasses the



following specific compound

wherein R¹

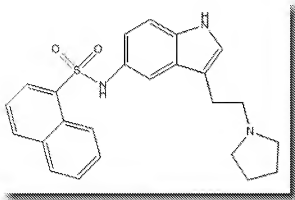
is NR⁸R⁹ and R⁸R⁹ together with the bridging nitrogen atom form a saturated heterocyclic ring,



specifically ; R²-R⁷ are hydrogen; and A is a polycyclic aromatic ring system, wherein the rings are 6 membered. Specifically, the above compound is disclosed in the instant

Specification as N-[1-(2-pyrrolidine-1-yl-ethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 78, Example 17) and the compound reads on claims 1-8 and 76-82.

7. *Merce-Vidal et al* teach compounds which are useful as 5-HT₆ modulators. In particular, *Merce-Vidal et al* disclose the compound N-{3-[2-(pyrrolidin-1-yl)-ethyl]-1H-indole-5-yl}-naphthalene-1-sulfonamide, having the following structure:



(Page 6, Example 45). Accordingly, the only

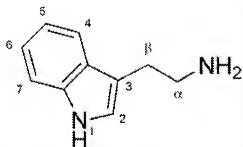
difference between the instant species and that taught by *Merce-Vidal et al* is the placement of $-(CH_2)_n-R_1$ (wherein $-(CH_2)_n-R_1$ in the instant invention and in *Merce-Vidal et al* are the same) on the indole core. As discussed previously, the compounds are thus positional isomers of each other, and the subtle difference between the compound taught by *Merce-Vidal et al* and the instantly claimed species is *prima facie* obvious in view of *In re Wilder*, 563 F.2d 457 (CCPA 1977).

8. Applicants, however, traverse this finding on the grounds that *In re Wilder* notes that such positional isomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties and, in the instant case, "even if it were the case that the claimed compounds are simply position isomers or homologs of the compounds disclosed by *Merce-Vidal et al*, Applicants... have provided bibliographic

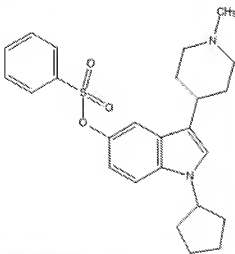
evidences... to provide that the different biological properties between 1-substituted and 3-substituted indoles are known from the prior art" (Applicant Argument, Page 7). Indeed, as noted by the court in *Takeda Chemical Industries, LTD. V. Alphapharm PTY., LTD.*, 492 F.3d 1350, citing *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound.' That is so because close or established '[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.' A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'" (at page 1356). However, the court (quoting *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985) also noted that "since our *Wilder* decision, we have cautioned 'that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious from one another'" (at page 1361) and that "in order to find a *prima facie* case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." (at page 1356). Thus, in *Takeda*, the court found no motivation existed in the prior art for one of ordinary skill in the art to modify a prior art compound (which was known at the time the invention was made to be toxic) by homologation and ring-walking to arrive at the claimed compound and wherein the claimed compound exhibited unexpectedly superior properties over the prior art compound.

9. Despite Applicants' assertions, the instant case is distinguishable from *Takeda* in that the prior art compound taught by *Merce-Vidal et al* differs from the instantly claimed compound in only one respect (i.e., ring walking the moiety from position 3 to position 1) whereas in *Takeda*, the compounds differed in two respects. Applicants, however, contend that "ring walking" encompasses not one change, but two changes since it entails "the introduction... at position 1" *and* "the elimination... from position 3" of the substituent (Applicant Arguments filed 8/21/2009, Page 11). Based on Applicants' view, the instant case is *still* distinguishable from *Takeda* in that the prior art compound taught by *Merce-Vidal et al* differs from the instantly claimed compound in only two respects (i.e., ring walking the moiety from position 3 to position 1 – which involves two changes) whereas in *Takeda*, the compounds differed in three respects (ring walking, which involves two changes, and homologation). Regardless, Applicants' argument is not found persuasive since it is understood that ring walking entails a single modification, even if it arguably involves two changes. Nor is Applicants' argument that "the skilled artisan would not consider the elimination of the specific substituent at position 3 in the compounds of *Merce-Vidal et al* could give compounds with 5HT₆ activity" since the second change (i.e., elimination of the substituent from position 3) disrupts the "tryptamine-like structure, which was widely held to be necessary for the 5HT₆ activity" (Applicant Argument filed 8/21/2009, Page 11) considered persuasive. As previously discussed, Example 28 in *Filla et al* (Page 67) does not appear to possess a tryptamine-like structure any more than the instantly claimed compound possesses said structure, yet Example 28 is disclosed as a 5-HT₆ modulator. Thus, it is not found persuasive that the skilled artisan would have expected maintaining the tryptamine-like structure in the compounds taught by *Merce-Vidal et al* to be critical for their

activity as 5-HT₆ modulators. Applicants indicate that Example 28 does, in fact, possess said structure. **Tryptamine** is represented by the following structure



(tryptamine) whereas **Example 28** has the following



structure

(Example 28). As such, Example 28

possesses a 3-aminocycloalkylindole structure, but not a 3-aminoalkylindole basic structure. Furthermore, whereas the amine group in tryptamine is a primary amine, the amine in Example 28 is a tertiary amine. In view of these two differences, it is not found persuasive that Example 28 possess a tryptamine like structure or that the skilled artisan would have expected maintaining the tryptamine-like structure in the compounds taught by *Merce-Vidal et al* to be critical for their activity as 5-HT₆ modulators.

10. The instant case is additionally distinguishable from *Takeda* in that, in the instant case, no where have Applicants provided evidence to suggest that the one difference in the instant case, i.e., the ring walking, was not a routine step in the drug optimization process at the time the instant invention was made (as was the case in *Takeda*; see page 1360).

11. Also, unlike in *Takeda*, the specific molecular modifications necessary to achieve the claimed invention are motivated in further view of *Filla et al*. As previously discussed, *Filla et al* teach compounds which (like *Merce-Vidal et al*) are 5-HT₆ modulators possessing an indole core. However, the compounds of *Filla et al* are substituted at position 1 of the indole core. Accordingly, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties (*Takeda* at page 1356) - would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT₆ modulators and possibly possess improved properties. Applicants, however, dispute this arguing that that *Filla et al* (which discloses 5-HT₆ receptor modulators possessing an indole core which is substituted at position 1) does not contain the exact substituent at position 1 as is disclosed by the prior art compound taught by *Merce-Vidal et al* (wherein the substituent is located at position 3) and recited by the instant claims. Nevertheless, *Filla et al* indicates that substitution of the indole core at position 1 does not disrupt the compound's activity as a 5-HT₆ modulator. The fact that the compounds taught by *Filla et al* do not contain the exact substituent at position 1 as is taught in the instant claims would not dissuade the person of ordinary skill in the art from making the compounds since the skilled artisan would seek to ring-walk to the substituent taught by *Merce-Vidal et al* to a position (such as position 1 as

taught by *Filla et al*) capable of supporting a similar substituent and maintaining activity as a 5-HT₆ modulator. As such, as discussed above, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties - would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT₆ modulators and possibly possess improved properties.

12. Finally, the instant case is distinguishable from *Takeda* in that there is nothing in the record to indicate that the instantly claimed compound possesses any unexpectedly superior properties over the prior art compound taught by *Merce-Vidal et al* such as, for example, reduced toxicity (as in *Takeda*) to overcome this *prima facie* rejection.

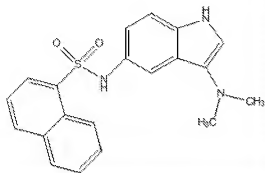
13. Applicants point to indole-containing compounds which are positional isomers of each other but which have distinct activities (Applicant Argument, Pages 8-9). However, Applicants' argument remains unpersuasive since, as previously noted, none of the compounds referenced are drawn to modulators of 5-HT₆. Furthermore, although it is clear that the referenced compounds are known to have different activities, it is not clear that the compounds also *lack* the same activity. That is, whereas compound (1) is claimed as an inhibitor of thromboxane A₂ synthesis in WO 9320065 while its positional isomer compound (2) is described as a selective h5-HT_{1D} receptor agonist, there is no evidence that compound (1) was assayed to evaluate its activity as a selective h5-HT_{1D} receptor agonist and was determined to not possess such activity, and *vice versa*. The same reasoning applies to the compounds relied on by Applicants at Pages 9-10; namely, there is nothing to suggest that the RN 137642-51-4 does not possess 5-HT₆ activity even though it is not indicated as such. Moreover, *assuming arguendo* that RN 137642-

51-4 does not possess such 5-HT₆ activity, since the compounds differ in three respects (two ring walking modifications and one halogen substitution; or five respects based on Applicants' view that a ring walking modification encompasses two changes) it would be impossible to ascertain whether the difference in activity was due to a single ring-walking modification as in the instant case.

14. Thus, since the instantly claimed compound differs from the prior art compound taught by *Merce-Vidal et al* by a single modification (i.e., is a positional isomer, compounds which *In re Wilder* teach are **generally** of sufficiently close structural similarity to possess similar properties), and since the single modification would have also been *prima facie* obvious in view of *Filla et al*, and since Applicants have not provided any evidence to suggest that the single modification was not a routine step in the drug optimization process at the time the instant invention was made, and since Applicants have also not introduced sufficient evidence to indicate unexpected properties of the claimed invention (such as reduced toxicity), Applicants have not overcome the presumption that positional isomers are **generally** of sufficiently close structural similarity that such compounds possess similar properties and the arguments are not found persuasive.

15. Accordingly, for all of the foregoing reasons, Applicants' arguments are not found persuasive. The rejection of claims 18-19, 46-47, 74-75, 84-85 and 92-93 in the previous Action and which are not specifically traversed beyond the traversals discussed above is maintained.

16. The rejection of claims 9 and 86-90 based on N-[3-(2-dimethylaminoethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 5, Line 3, Example 8) having the following structure:



in the previous Action is also maintained for the same reasons as discussed above.

Claim Objections

17. Claims 83 and 91 are objected to as depending from a rejected base claim.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614